Testimony
Before the
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives

Improving America's Health: Examining Federal Research Efforts for Pulmonary Hypertension

Statement of

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Major points – December 8, 2005, Testimony of Dr. Mark Gladwin to the House Energy and Commerce Subcommittee on Health

- Over the past decade, several drugs that affect vessel dilation and constriction have received FDA approval. The first drugs available were given via injection, but three drugs recently have been approved that can be inhaled or swallowed.
- Researchers now believe that pulmonary hypertension also is caused by a cancer-like proliferation of smooth muscle cells of the pulmonary artery and hypothesize that anti-cancer drugs may have applications as therapies for pulmonary hypertension patients.
- In FY 2005, the NHLBI research portfolio included more than 90 research and training projects on pulmonary hypertension. The Institute also issued a Request for Applications for 3 or 4 pulmonary vascular disease research centers. In FY 2006, the NHLBI plans to launch a new program to test whether sildenafil therapy is beneficial for patients who have pulmonary hypertension in conjunction with sickle cell anemia.
- The NHLBI started a new research effort, the Vascular Medicine Branch, in the Division of Intramural Research. Under the leadership of Dr. Gladwin, the branch has four major goals:
  - Development of new therapies for pulmonary hypertension.
  - Testing of whether sildenafil therapy can halt blood vessel damage that causes patients who have sickle cell anemia or thalassemia to develop pulmonary hypertension.
  - Identification of "pre-disease" in high-risk patients.
  - Development of clinical trials of compounds to reverse the cancer-like proliferation of smooth muscle cells.

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Mr. Chairman and members of the Subcommittee, thank you for the opportunity to appear before you today to discuss research on pulmonary hypertension conducted by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, an agency of the U.S. Department of Health and Human Services. Today I will briefly outline what we know about the basic biology of pulmonary hypertension, summarize our research efforts to develop new treatments and detection strategies, and describe our vision for future research activities.

Pulmonary hypertension is a disabling condition caused by a narrowing of the small arteries that carry blood through the lungs, resulting in damage to the heart. As the arteries tighten, the heart must work harder to pump blood through them. Pulmonary hypertension can manifest itself as rapid heart rate, dizziness, shortness of breath, chest pain, fatigue, and fainting—symptoms so general that the disease is often not diagnosed until the overworked heart muscle has become too weak to pump enough blood through the lungs and the patient is unable to perform even the simplest daily activities. Pulmonary hypertension can be fatal, but new treatments are available that can slow its progression and improve quality of life.

The disease exists in two forms: primary pulmonary hypertension (PPH), which arises without any clear-cut underlying illness to precipitate it, and secondary pulmonary hypertension, which is caused by another illness such as sickle cell anemia or HIV infection. Basic, translational, and clinical studies have led to the discovery of two

different mechanisms common to both forms of the disease: (1) blood vessel dilation/constriction; and (2) blood vessel blockage.

The first mechanism involves some chemicals released from the lining of blood vessels (called the endothelium) that open up or dilate blood vessels and other opposing chemicals that constrict the blood vessels. Dilating chemicals include prostacyclin (the compound for which the Nobel Prize in Physiology or Medicine was awarded in 1982) and nitric oxide (the subject of the 1998 Nobel Prize in Physiology or Medicine). Both are potent biological molecules that not only open up blood vessels but also block clotting and abnormal cellular growth. They are opposed by potent constrictors such as endothelin, a chemical that is structurally very similar to sarafotoxins found in snake venom.

Over the past decade, several drugs that attenuate these vasoconstrictor chemicals have been developed and have received FDA approval. Discovery of these drugs led to a revolution in therapy and provided new hope for patients by reducing symptoms, increasing exercise capacity, and improving survival. The first of these drugs, however, has to be given through a permanent catheter placed in a vein in the neck and connected to a battery-powered iced pump. Treatment became a little easier for some patients in 2002 when the FDA approved a second, more stable drug that could be infused under the skin (thereby reducing a patient's likelihood of infection) and, because the drug did not need to be chilled, could be administered by a mini-pump that was not heavily weighed down by ice. Over the past 12 months, three additional drugs that are even easier for

patients to take have been approved for treatment of pulmonary hypertension: iloprost (Ventavis®), which can be inhaled through a nebulizer, and bosentan (Tracleer®) and sildenafil (Viagra®), which are swallowed as pills. Furthermore, these recent advances have opened the door to an avalanche of new related medications with different receptor targets, different half-lives, and different side-effect profiles.

The existing medications clearly improve the quality of life and increase survival, but they do not and cannot cure the disease because they act only on the first critical mechanism of pulmonary hypertension. Researchers now believe that the devastating blood pressure increase in pulmonary vessels also is caused by an abnormal, almost cancerous (though not metastatic, i.e., not spreading to other tissues), proliferation of the smooth muscle cells of the pulmonary artery that crowds the blood vessel and eventually chokes off all blood flow. Scientists are building on advances in treatments for patients who have cancer or coronary heart disease as they search for compounds that can interfere with the cancer-like growths and thereby not only prevent disease progression but also cure the disease by reversing vessel obstruction.

Many of those efforts are funded by the NHLBI, which supports a robust research effort in pulmonary hypertension. In Fiscal Year (FY) 2005, our research portfolio included more than 90 research and training projects on pulmonary hypertension that address the problem from multiple perspectives. In FY 2005, we also requested grant applications for 3 or 4 pulmonary vascular disease research centers. These centers will fuse basic research, studies of pre-clinical animal models, and human clinical trials to

expedite development of the next generation of therapeutics. During FY 2006, we plan to launch a new program to test whether sildenafil therapy is beneficial for patients who have pulmonary hypertension in conjunction with sickle cell anemia. And because most of our best ideas come from individual investigators who submit grant applications, we are committed to maintaining the financial flexibility to fund the most promising grant applications.

We have also started a new research effort in the intramural division of the NHLBI that I am leading in the Vascular Medicine Branch. This important bench-to-bedside initiative has four major goals:

1) Development of new therapies for pulmonary hypertension. We currently are recruiting patients for five phase I/II trials and are launching two phase III studies this year. We have identified a new medication, nitrite, that can be nebulized easily with current asthma-delivery devices and can decrease pulmonary pressures in animal models of neonatal pulmonary hypertension[1].

2) Testing of whether sildenafil therapy can halt blood vessel damage that causes patients who have sickle cell anemia or thalassemia to develop pulmonary hypertension. We have discovered that patients with sickle cell disease and thalassemia are developing pulmonary hypertension at an alarming rate[2,3]. One-third of these patients, almost 20,000

[1] Hunter CJ, Dejam A, Blood AB, Shields H, Kim-Shapiro DB, Machado RF, Tarekegn S, Mulla N, Hopper AO, Schechter AN, Power GG, **Gladwin MT**. Inhaled nebulized nitrite is a hypoxia-sensitive NO-dependent selective pulmonary vasodilator. Nature Medicine. October 2004; volume10, issue 10: pages 1122-1127.

[2] **Gladwin MT**, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder WC, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. New England Journal of Medicine. February 26, 2004; volume 350, issue 9: pages 886-895.

Americans, have pulmonary hypertension, which represents the greatest risk for death in this population.

3) Identification of "pre-disease" in high-risk patients. As is the case with diabetes and high blood pressure, early therapy has the potential to prevent end-organ complications. We are developing screening biomarkers and strategies for patients at high risk of developing pulmonary hypertension, such as those who have scleroderma, HIV, or sickle cell disease, so that early disease can be identified and addressed.

4) Development of phase I/II trials using chemotherapeutic medications and novel small molecules to reverse the cancerous proliferation of smooth muscle cells in the blood vessels of the lung. We believe such "anti-proliferative" therapy is the key to an ultimate cure.

Thanks to the efforts of researchers and patient advocates and the support of Congress and the American taxpayers, pulmonary hypertension is moving from the ranks of diseases that once were considered to be untreatable to the growing list of conditions for which medical science offers hope of a better quality of life and more years to enjoy it. Our goal is to restore to health those who suffer from pulmonary hypertension and to prevent others from developing this dreadful disease.

Thank you for being committed to this noble cause and for allowing me to speak with you today. I will be happy to answer any questions you may have.

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[3] Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, Hazen SL, Vichinsky EP, Morris SM Jr, **Gladwin MT**. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA – Journal of the American Medical Association. July 6, 2005; volume 294, issue 1: pages 81-90.

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Mark Gladwin received his Doctor of Medicine from the University of Miami Honors Program in Medical Education in 1991. After completing his internship and chief residency at the Oregon Health Sciences University in Portland, Oregon, Dr. Gladwin joined the National Institutes of Health (NIH) in 1995 as a critical care fellow at the Clinical Center. After a one-year clinical fellowship in pulmonary medicine at the University of Washington in Seattle, he returned to the NIH Clinical Center for a research fellowship in the Critical Care Medicine Department under the mentorship of Drs. James Shelhamer, Frederick Ognibene, Alan Schechter, and Richard Cannon.

In 2005, Dr. Gladwin was appointed Chief of the new Vascular Medicine Branch in the Division of Intramural Research at NIH's National Heart, Lung, and Blood Institute (NHLBI). As branch chief, he oversees a robust portfolio of studies to define the cellular and molecular mechanisms that underlie normal physiological function and disease processes of the lungs and their vasculature and fosters collaborations with researchers in the NIH Clinical Care Medicine Department to ensure strong and smooth interactions among laboratory and clinical investigations.

He has been involved in enrolling more than 700 patients in more than a dozen studies at the NIH Clinical Center and has co-authored 82 published peer-reviewed manuscripts addressing biochemical mechanisms involved in blood vessel relaxation and contraction. Recent efforts to develop a mechanistic, clinical, and epidemiological description of hemolysis-associated pulmonary hypertension led to the observation that pulmonary hypertension occurs in 30 percent of patients who have sickle cell disease, is a major cause of mortality in this patient population, and is strongly associated with excessive destruction of red blood cells, high levels of iron in the blood, and kidney disease. These findings, combined with his earlier mechanistic studies, are leading to clinical trials of compounds that can help patients have pulmonary hypertension in conjunction with sickle cell anemia or other disorders.